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Title : Association of an anti-atherothrombotic agent and an anti-platelet-aggregation agent

Art Unit : 1625

Examiner : T. V. OH

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.132

I, Laurence LEROND, a citizen of France, 20, avenue La Bruyère, 78160 Marly-Le-Roi, France, declare and say that :

I hold the degree of Doctor in Pharmacy from the University of Paris V, France, in 1982.

Since November 1993 I have been working in Institut de Recherches Internationales Servier :

- From February 1993 to December 2001 as a Head of Biological Studies in the Therapeutic Research Department of Angiology, in charge of preclinical Development of various drugs intended for use in Vascular Diseases.
- From January 2002 until present as Head of Department in the Therapeutic Research Department of Vascular Diseases then in the Cardiovascular Therapeutic Research Unit. Since October 2001, I have been responsible for the non-clinical development of S 18886 and since November 2003 for the non-clinical and human pharmacokinetic development of S 18886.

I am the author or co-author of 3 patents and 8 international publications devoted to Vascular Biology.

I am one of the co-inventors of the instant application concerning an "association of an anti-atherothrombotic agent and an anti-platelet-aggregation agent".

I am thoroughly familiar with the above-mentioned patent application and I fully support the conclusions derived and the arguments presented as concerns the therapeutic interest of the compounds described.

The association of the present invention, compound A with clopidogrel, shows a synergy in terms of anti-thrombotic activity. The association according to the invention is accordingly useful in the treatment of cardiovascular illnesses such as acute coronary syndrome, stable or unstable angina, endothelial dysfunction, vascular illnesses associated with atherosclerosis, hypertension, diabetes and heart failure, and in the prevention and treatment of disorders of the vascular, cardiovascular or neurovascular system and of thrombo-embolic disorders associated especially with atherosclerosis, auricular fibrillation and invasive surgical procedures in cardiology, neurology, vascular pathology and radiology.
This association allows an improvement in the anti-thrombotic effect evaluated by the inhibition of collagen-induced platelet aggregation *ex vivo* which is shown by the test described in the present application (US Serial 10/574,119), at page 5, lines 1 to 8.

The association disclosed in the present application (US Serial 10/574,119) allows substantial synergy to be obtained in terms of activity, which could not have been foreseen from any teaching of the literature.

It is the position of the Office that based on the disclosures of Lavielle, et al. and Ogletree, et al., one skilled in the art would have been motivated to replace the thromboxane A2 receptor antagonist, such as ifetroban, with compound (A) of formula (I) to arrive at the instantly claimed composition.

Ogletree, et al. does indeed describe a composition containing an ADP receptor inhibitor, such as clopidogrel, and a thromboxane A2 receptor antagonist, such as ifetroban, for use in the treatment of cardiovascular diseases.

We will provide a demonstration of superior and unexpected effects associated with the instantly claimed combinations compared to the combinations disclosed in Ogletree, et al.

Ifetroban is a compound, which is not commercially available. Moreover, as the synthesis of ifetroban is a very complex synthesis we weren't able to obtain this compound.

Ramatroban (or BAYu3405) is a compound, which is commercially available and is also described in Ogletree *et al.* as a thromboxane A2 receptor antagonist and specifically claimed in claim 5 of Ogletree et al.

Therefore, we have compared the association of compound (A) of formula (I) + clopidogrel with the association of ramatroban + clopidogrel.

In fact, Ogletree *et al.* disclose pharmaceutical combination comprising an ADP-receptor blocking antiplatelet drug (preferably clopidogrel), and a thromboxane A2 receptor antagonist (preferably ifetroban) for use in the treatment of cardiovascular diseases. Besides, Lavielle *et al.* disclose specifically the structure of compound (A) and its pharmacological properties as a thromboxane A2 receptor antagonist.

In order to overcome this objection, please find enclosed comparative data showing that the combination of compound (A) with clopidogrel presents unexpected effects that could not be anticipated from prior art. It is noteworthy that ifetroban is not commercially available and that its synthesis is very complex. Consequently, it was more convenient to compare the association of clopidogrel + compound (A) with the association of clopidogrel + ramatroban (also called BAYu3405). This latter compound, which is described and claimed in Ogletree *et al.* (see claim 5), is a thromboxane A2 receptor antagonist that is already marketed.

Materials and Methods

The thrombosis model used in this study has been recently published (Adaptation of the Folts and electrolytic methods of arterial thrombosis for the study of anti-thrombotic molecules in small animals by Sturgeon SA, Jones C, Angus JA and Wright CE in J Pharmacol Toxicol Methods; 2006, 53, 20-29).

CD rats were anesthetized with pentobarbital (50 mg/kg IP) and placed on a thermoregulated blanket. A tracheotomy is performed to facilitate breathing. A 1 mm Doppler sensor is placed around a carotid artery and blood flow was recorded (Transonics T 206 and Acknowledge). After 5 minutes of stabilisation, the carotid artery diameter is reduced with a silk suture (6/0 - Ethicon) to stabilise the blood flow at 50% of its initial value. Then, the vessel was clamped 5 times during 20 seconds each time on the suture. The resulting decrease of the flow is a sign that a blood clot has formed (also called thrombus).The occlusion time was noted (flow=0 during 1 minute). The blood clot is then mechanically dislodged by clamping the artery 3 to 4 times on the suture. These periods of flow reduction (Cyclic Flow Reduction or CFR) can be processed and the effect of an anti-thrombotic treatment can be determined.

In control rats, the time to the first occlusion as well as the number of CFR occurring within 60 minutes were noted. As showed on Figure 1, the time to the first occlusion is of 5.5 ± 0.4 min and the number of CFR is of 11.2 ± 0.3 min / 60 min.

Results

In order to evidence a synergistic effect either between the compounds of the association [clopidogrel + compound (A)] or between the compounds of the association [clopidogrel + BAYu3405], the following treatments were administered to the animals :

- clopidogrel : 0.03 mg/kg, force-feeding of 5 ml/kg, 24 and 2 hours before stenosis,
- compound (A) of formula (I) or BAYu3405 : 0.3 mg/kg, force-feeding of 5 ml/kg, 1 hour before stenosis,

Animals are treated either with one of the compounds, either with [clopidogrel + compound (A)], or with [clopidogrel + BAYu3405].

The results are displayed in following Figures 1 and 2:

Figure 1 : Effect of clopidogrel (Clopi) alone, of BAYu3405 alone, and of their association on the arterial thrombosis parameters in rat.

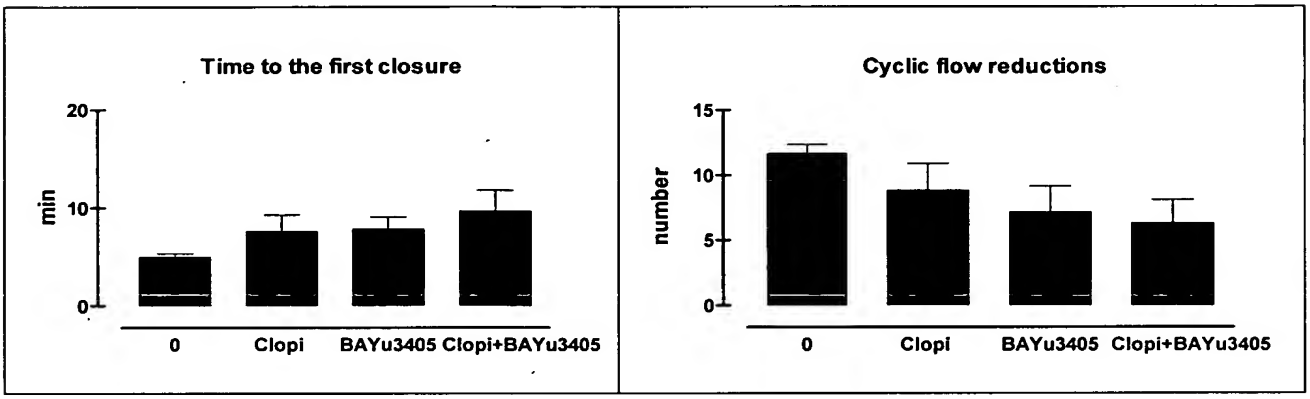
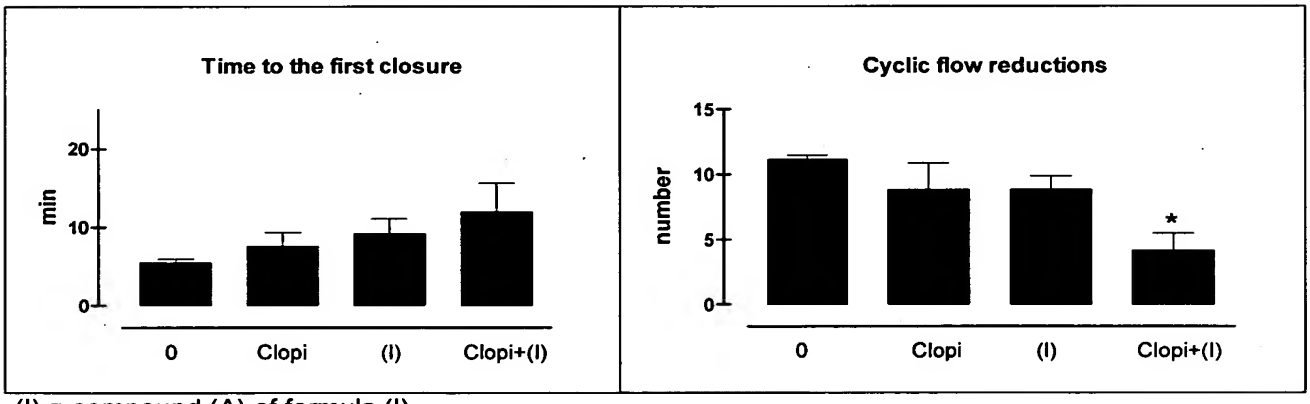


Figure 2 : Effect of clopidogrel (Clopi) alone, of compound (A) alone, and of their association on the arterial thrombosis parameters in rat.



(I) = compound (A) of formula (I)

1. The treatment with clopidogrel alone has slightly, but not significantly, influenced the two following parameters (see Figures 1 & 2):

- the time to the first occlusion is of 7.6 ± 1.7 min (5.5 ± 0.4 min with control rats),
- the number of CFR is of 8.8 ± 2.1 min / 60 min (11.2 ± 0.3 min / 60 min with control rats).

2. The treatment with BAYu3405 alone has slightly, but not significantly, influenced the previously mentioned parameters (see Figure 1):

- the time to the first occlusion is of 7.8 ± 1.3 min (5.5 ± 0.4 min with control rats),
- the number of CFR is of 7.2 ± 2.0 min / 60 min (11.2 ± 0.3 min / 60 min with control rats).

3. The treatment with compound (A) alone has slightly, but not significantly, influenced the previously mentioned parameters (see Figure 2):

- the time to the first occlusion is of 9.2 ± 1.9 min (5.5 ± 0.4 min with control rats),
- the number of CFR is of 8.8 ± 1.0 min / 60 min (11.2 ± 0.3 min / 60 min with control rats).

4. The association [clopidogrel + BAYu3405] does not show any synergistic effect compared to the effect observed with the two compounds used separately (see Figure 1):

- the time to the first occlusion is of 9.7 ± 2.1 min (5.5 ± 0.4 min with control rats),
- the number of CFR is of 7.2 ± 2.0 min / 60 min (11.2 ± 0.3 min / 60 min with control rats).

5. The association [clopidogrel + compound (A)] induces a remarkable synergy as to the antithrombotic effect compared to the effect observed with the two compounds used separately (see Figure 2):

- the time to the first occlusion increases up to 12.0 ± 3.6 min (5.5 ± 0.4 min with control rats),
- the number of CFR decreases significantly down to 4.2 ± 1.3 min / 60 min (11.2 ± 0.3 min / 60 min with control rats).

Conclusion

The compound (A) used alone at the dose of 0.3 mg/kg seems to induce a slightly lower anti-thrombotic effect compared to BAYu3405 used at the same dose. But, it is noteworthy that an important synergy was observed for the association [clopidogrel + compound (A)], which is not the case for the association [clopidogrel + BAYu3405].

These data evidence that there is a synergy between clopidogrel and the compound (A) in the treatment of arterial thrombosis. Such a synergy does not happen with the association [clopidogrel + BAYu3405] described in Ogletree *et al.* wherein only venous thrombosis has been studied. In addition, the study in man disclosed in our patent application (see page 5) shows that the association [compound (A) + clopidogrel] has an anti-aggregation effect. Considered all together, our results are all the most relevant since platelets are very involved in arterial thrombosis, whereas they play a less crucial role in venous thrombosis. In addition, it should be noted that in the present study, compounds have been administered per oral route (*versus* intravenous route in Ogletree *et al.*).

In summary

(1) The association [clopidogrel + compound (A)] displays an activity and a synergy in arterial thrombosis (whereas Ogletree *et al.* deals with venous thrombosis).
(2) The association [clopidogrel + compound (A)] is also active and synergistic in platelet aggregation in man (see page 5 of the present patent application).
(3) The association [clopidogrel + compound (A)] is active per oral route in rat and in man (in Ogletree *et al.,* ifetroban is administered intravenously).
(4) The association [clopidogrel + compound (A)] is more efficient than the association [clopidogrel + BAYu3405] in arterial thrombosis model in rat, this latter model being relevant as regards to human thrombosis.

Consequently, claims 12 to 24 are not obvious in light of disclosures of Ogletree *et al.* and Lavielle *et al.*

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of the title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not

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Executed at: Courbevoie

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